

A Novel Biologic Hemostatic Dressing (Fibrin Patch) Reduces Blood Loss and Resuscitation Volume and Improves Survival in Hypothermic, Coagulopathic Swine With Grade V Liver Injury

Angel V. Delgado, PhD, Bijan S. Kheirabadi, PhD, Todd M. Fruchterman, MD, PhD, Michael Scherer, BS, Douglas Cortez, Charles E. Wade, PhD, Michael A. Dubick, PhD, and John B. Holcomb, MD

Objectives: This study evaluated the efficacy of a biologic hemostatic fibrin patch (FP) to control coagulopathic bleeding and prevent death in a porcine model of severe liver injury with hemodilution and hypothermia.

Methods: Coagulopathy was produced in swine by exchanging 60% of the animals' circulating blood volume with Hextend and lowering the core temperature to $32.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. A grade V liver injury was induced and allowed to bleed freely for 30 seconds (pretreatment blood loss). Animals were randomly divided into three treatment groups: hepatic packing (HP) using laparotomy sponges, FP application plus HP, or placebo patch (PP) application plus HP. Animals were resuscitated

to 80% of the preinjury mean arterial pressure. Core temperature, mean arterial pressure, and survival were monitored for 1 hour postinjury. Patches were removed from the animals that survived to 1 hour and they were monitored for an additional hour.

Results: Coagulopathy was confirmed by significant increases ($p < 0.01$) in prothrombin time, activated partial thromboplastin time, and activated clotting time in preinjury measurements as compared with baseline values. Pretreatment blood loss was not different among the groups. However, significant ($p < 0.01$) differences were observed in the posttreatment blood loss ($772 \text{ mL} \pm 340 \text{ mL}$, $4,977 \text{ mL} \pm 440 \text{ mL}$, $4,173 \text{ mL} \pm 608 \text{ mL}$), as well as the required fluid resuscitation volume ($994 \text{ mL} \pm 26 \text{ mL}$, $4,083 \text{ mL} \pm 185 \text{ mL}$, $3,494 \text{ mL} \pm 492 \text{ mL}$), between FP versus PP or HP groups, respectively. In addition, 89% of FP animals survived the 2-hour observation with an average survival time of $111 \text{ minutes} \pm 9 \text{ minutes}$, which was significantly higher than the PP (0% survival, $39 \text{ minutes} \pm 4 \text{ minutes}$) or HP (13% survival, $41 \text{ minutes} \pm 12 \text{ minutes}$) groups.

Conclusion: FP with packing effectively controlled coagulopathic bleeding and prevented death in a model of grade V liver injury in which HP alone (standard of care) was ineffective.

Key Words: Hemorrhage, Coagulopathy, Hypothermia, Hemostasis, Dressing, Swine.

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Hemorrhage is a major cause of death in civilian trauma patients and is the principal cause of death on the battlefield.¹ Frequently, such hemorrhage is complicated by hypothermic and dilutional coagulopathies, conditions described in wounded soldiers.^{2,3} The pathogenesis of severe posttraumatic coagulopathy is complex and multifactorial, but is commonly the result of platelet (PLT) and coagulation factor loss, consumption, or dysfunction. In addition it may be exacerbated by dilution, acidosis, and hypothermia.

Thus, virtually every aspect of the normal coagulation cascade is affected in a trauma patient who is cold, acidotic, and exsanguinating.^{4–7} A hemorrhage control technique able to achieve rapid hemostasis, especially in the presence of a coagulopathy, would also reduce resuscitation requirements and improve outcomes.

The primary objective of this study was to determine the effect of a fibrin patch (FP) on control of hemorrhage in anesthetized, coagulopathic pigs, subjected to severe liver injury. Secondary objectives were to determine effects of the FP on: (1) percent survival, (2) survival time, and (3) fluid resuscitation requirements. The FP used in this study was a combination product composed of a unique composite matrix with a layer of dried human fibrinogen (FIB) and human thrombin in a $4 \times 4 \text{ in.}$ patch. The placebo patch (PP) consisted of the same composite matrix with equal amount of freeze-dried human albumin equivalent to the total biologic material found in the FP, also measuring $4 \times 4 \text{ in.}$ The coagulopathic liver injury model has been used previously to evaluate other hemostatic dressings.^{8,9} Our hypothesis was that the FP would reduce posttreatment blood loss, thereby reducing resuscitation fluid requirements and improve survival compared with standard of care and placebo treatments. The FP is completely bioabsorbable so that it could be left in

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From the US Army Institute of Surgical Research (A.V.D., B.S.K., M.S., D.C., C.E.W., M.A.D. J.B.H.), San Antonio, Texas; and Ethicon (T.M.F.), Somerville, New Jersey.

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Address for reprints: Library Branch, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX 78234-6315; email: angel.delgado@amedd.army.mil.

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a patient after application, providing the additional benefits of an undisturbed clot and a reduction in the total number of operations. Clinically, this FP could translate into reductions in intensive care unit stay, rate of infection, morbidity, mortality, and overall cost.

MATERIALS AND METHODS

Animals and Surgery

Crossbred male and female Yorkshire swine (38.2 kg \pm 3.3 kg body weight) were fasted for approximately 24 hours before surgery, but water was allowed *ad libitum*. Animals were maintained in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. The Institutional Animal Care and Use Committee of the US Army Institute of Surgical Research, Fort Sam Houston, TX, approved this study. Animals received humane care in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication 86-23, revised 1996).

On the day of study, pigs were sedated using a combination of glycopyrolate 0.01 mg/kg and Telazol 6 mg/kg, and intubated. Anesthesia was maintained with 2% to 3% isoflurane in 100% oxygen, utilizing a closed circuit system. A stable plane of anesthesia was maintained and ventilatory and anesthetic parameters were adjusted to attain the end-tidal pCO_2 of 40 mm Hg. The carotid artery and jugular vein were cannulated for monitoring and recording of vital signs and infusion of resuscitation fluid. The right femoral artery was also cannulated for controlled hemorrhage and induction of dilutional coagulopathy as described below. A midline laparotomy was then performed; the liver was inspected grossly for obvious abnormalities, and a splenectomy and cystostomy were performed. Lactated Ringer's solution (37°C) was administered three times the weight of the spleen to offset blood loss associated with spleen removal.

Coagulopathy Induction

Hypothermia and dilutional coagulopathy were induced as previously described.⁸ Briefly approximately 60% of the animals' estimated total blood volume was withdrawn from the femoral catheter and replaced with an equal volume of 25°C Hextend intravenously (i.v.). Hypothermia with the target temperature of 32°C \pm 0.5°C was also achieved by 25°C Hextend infusion and additional external cooling. Coagulopathy was defined as a significant increase in activated clotting time (ACT), prothrombin time (PT), and activated partial thromboplastin time (aPTT) time, and a significant decrease in hematocrit (HCT), PLT count, FIB concentration, and temperature.

Liver Injury and Resuscitation

Liver injury was created by using a custom designed clamp with x-shaped blades as described previously.¹⁰ The injury completely penetrated the liver, with one or more of the left, medial, right hepatic veins in the medial lobe, and

portal vein being lacerated. The exact number of the veins lacerated was used to score the injury severity in each experiment. During the first 30 seconds after injury, shed blood was collected by suction. This blood volume was measured and designated as pretreatment blood loss.

Immediately after this 30-second bleeding period, resuscitation was initiated by infusing warm (37.0°C \pm 1.0°C) Hextend in the animals. Fluid was administered into the jugular vein at a rate of 150 mL/min until mean arterial pressure (MAP) reached 80% of the preinjury MAP. This was designated as the target MAP. The resuscitation fluid infusion was not started again until the animal's MAP dropped 10% from the target MAP. Hextend resuscitation to maintain blood pressure at 80% of the preinjury MAP was discontinued at 60-minute posttreatment time and the total volume was recorded.

Experimental Design

Animals were assigned randomly to one of the three treatments. The surgeon was blinded to treatment throughout the study for FP (n = 9) and PP (n = 9). In the case of the hepatic packing (HP, n = 8) group, the surgeon was kept blinded until the treatment time. Simultaneously with the start of resuscitation, FP or PP dressings were applied. One dressing was applied to the visceral surface of the quadrate lobe and three additional dressings were placed into the injury from the diaphragmatic aspect with 3 minutes of manual compression. In the HP group, manual compression was also applied to the liver for 3 minutes. At the end of the compression, livers were packed with sterile 18 in. \times 18 in. four-ply laparotomy sponges (11-14 pads as needed) in all three groups. Once the peri-HP was complete, the abdomen was partially closed to the midway point with towel clamps and monitoring began.

Animals were monitored for up to 120 minutes postinjury. Hemostasis was defined as the absence of visible bleeding in and around the injury site. Animals that survived the initial 60-minute period were reopened and all laparotomy sponges removed and hemostasis was observed. The abdomen was closed again with sutures and pigs were monitored for an additional 60-minute period. At the end of the second observation period (120 minutes total time), surviving animals were killed with an intravenous overdose of a sodium pentobarbital-based veterinary euthanasia solution (Fatal Plus, Fort Dodge, IA).

Immediately after death, the vena cava was clamped just above the liver. Blood, blood clots, and preweighed laparotomy sponges were collected from the peritoneal cavity and weighed to determine posttreatment blood loss. The liver was then excised and the dressing's attachment strength was measured with a calibrated CS200 digital crane scale (Intercomp Co. Minneapolis, MN). The liver was carefully examined and the injury scored based on the number of vessels lacerated was determined.

Data Analysis

Data analyses were performed using SAS, version 8.1.¹¹ Data (such as HCT, ACT, PT, aPTT, FIB, and pH) measured at different times were analyzed using a mixed model analysis of variance, allowing for treatment, time, and treatment by time interaction as fixed effects and replicate subject as a random effect. The covariance structure for the mixed model was determined using Bayesian Information Criterion. Hochberg's step-up Bonferroni method was used for *p* value adjustment for multiple comparisons among treatments at each time point and among time points within each treatment, respectively.¹² Continuous data measured at a single time point (such as MAP, pretreatment blood loss, posttreatment blood loss, and resuscitation fluid volume) were analyzed using one-way analysis of variance. Dunnett's method was used for the *p* value adjustment for multiple comparisons with the FP group. Survival time and survival rate were analyzed by the log rank test and Fisher's exact test, respectively. Injury score and packing number were considered discrete data and were analyzed using appropriate nonparametric tests. *p* < 0.05 was considered significant; the data are expressed as mean ± SEM.

RESULTS

A total of 28 animals were entered into this study. One animal was excluded because of excessive blood loss during the splenectomy procedure and another because of an injury not severe enough to meet the inclusion criteria. This resulted

in 26 experimental animals of 9 each in the FP and PP groups and 8 in the HP group.

Baseline parameters including animal weight (38.4 kg ± 0.9 kg), estimated total blood volume (2,690 mL ± 75 mL),⁸ initial body temperature (37.3°C ± 0.1°C), and pH (7.43 ± 0.01) were similar among all treatment groups. Baseline coagulation and complete blood count variables, including ACT, PT, aPTT, FIB, PLT, and HCT, showed no statistically significant differences among treatment groups (Table 1). All animals had coagulation function values that were within the normal ranges. After isovolemic hemodilution, compared with baseline, core temperatures, HCT, PLT, and FIB decreased significantly whereas ACT, PT, and aPTT increased significantly for all animals with no statistically significant differences among treatment groups (Table 1). These measurements demonstrated that all animals across groups developed a similar degree of dilutional coagulopathy. In addition, the animals were cooled equally to hypothermic temperature of 32.1°C ± 0.1°C with no differences among groups.

After coagulopathy, all animals received a grade V liver injury with a large 10 × 8 × 4 cm penetrating parenchymal wound and laceration of an average of two major central hepatic veins (Table 2). There were no significant differences among treatment groups. The physiologic response to injury was the same in all groups. The mean blood loss during the 30 seconds immediately after injury (pretreatment blood loss) was 441 mL ± 30 mL in the FP group, 518 mL ± 53 mL in the PP, and 581 mL ± 61 mL in the HP group with no

Table 1 Core Temperatures, Coagulation Parameters, Hematocrit, and Platelet Counts of Pigs Before (Baseline, BL) and After Hemodilution and Hypothermia (Preinjury, PI)

Time Point	Treatment	Temperature	ACT	PT	aPTT	FIB	HCT	PLT
BL	FP	37.2 ± 0.1	99 ± 2	10.7 ± 0.2	16.1 ± 0.2	142.1 ± 7.1	30 ± 1	307 ± 28
BL	HP	37.4 ± 0.2	100 ± 3	10.8 ± 0.2	15.6 ± 0.1	159.0 ± 8.3	27 ± 1	281 ± 37
BL	PP	37.2 ± 0.1	102 ± 2	10.4 ± 0.1	15.8 ± 0.2	180.9 ± 7.3	29 ± 1	285 ± 22
PI	FP	32.0 ± 0.1*	134 ± 3*	15.1 ± 0.3*	20.8 ± 0.3*	97.0 ± 4.3*	14 ± 0.4*	106 ± 11*
PI	HP	32.2 ± 0.1*	131 ± 2*	14.6 ± 0.3*	20.6 ± 0.5*	97.5 ± 3.8*	14 ± 0.0*	120 ± 12*
PI	PP	32.2 ± 0.1*	141 ± 6*	14.8 ± 0.3*	20.1 ± 0.4*	97.2 ± 4.2*	14 ± 0.5*	105 ± 10*

Average baseline (BL) and preinjury (PI, posthemodilution and hypothermia), measurements of activated clotting time (ACT) (s), prothrombin time (PT) (s), activated partial thromboplastin time (aPTT) (s), fibrinogen (FIB) concentration (mg/dL), hematocrit (HCT) (%), and platelet (PLT) counts (10³/μL) in pigs. Values are the mean ± SEM.

* Statistical significance compared with baseline (*p* < 0.01) within each group.

Table 2 Injury and Posttreatment Period Parameters

Treatment	n	Injury Score*	Resuscitation Achieved MAP†	Resuscitation Fluid‡	Total Posttreatment Blood Loss§
FP	9	2.0 ± 0.3	68 ± 4.1	994 ± 265	772 ± 340
HP	8	2.0 ± 0.3	40 ± 4.1	3494 ± 492	4173 ± 608
PP	9	2.0 ± 0.4	45 ± 3.7	4083 ± 185	4977 ± 440

* Injury Score represents average number of hepatic veins lacerated by the injury in the medial lobe of livers.

† Resuscitation achieved MAP, MAP (mm Hg) that was reached by Hextend resuscitation.

‡ Resuscitation fluid, total resuscitation fluid volume (mL) infused during the first hour after treatment.

§ Total posttreatment blood loss, total blood loss (mL) during the 2-h observation period after hemostatic treatment.

|| Statistically different than HP or PP group, *p* < 0.01.

significant difference among groups. Likewise, mean percentage drops in blood pressure from baseline to 30 seconds after injury were $30.0\% \pm 3.1\%$, $26.0\% \pm 4.5\%$, and $33.5\% \pm 5.2\%$ for the FP, PP, and HP respectively. After 3-minute treatment or compression, livers were successfully packed and Hextend was administered that restored the MAP to the targeted levels. The number of gauze packing sponges used (12.3 ± 0.5) and the resuscitation target MAP (62.6 mm Hg ± 1.5 mm Hg) were not different among treatment groups.

In the FP-treated animals, complete hemostasis was initially achieved in 100% of the animals after the 3-minute compression period. However, in one case, hemostasis was unstable and bleeding occurred after partial closure of the abdomen. The failure in this case might have been caused by the incomplete coverage of injured tissue and lacerated vessels with the dressings. It was often difficult to cover the entire wound with dressings because of the complexity and irregular (stellate) shape of hepatic wounds. The hemostatic treatments in the other groups did not achieved hemostasis in any of the animals. The total posttreatment blood loss was 772 mL ± 340 , $4,977$ mL ± 440 mL, and $4,173$ mL ± 608 mL for FP, PP, and HP, respectively. Compared with PP and HP, FP significantly reduced blood loss by an average of 83% ($p < 0.01$). Bleeding was minimal (119 mL ± 17 mL) after removal of packs from the eight surviving pigs in FP group. Whereas unpacking of the liver in the only 60-minute surviving pig in the other groups resulted in a significant blood loss ($1,094$ mL) in the second hour of observation (Fig. 1). Only FP-treated animals achieved and maintained the resuscitation target MAP during the 60-minute observation period. The average MAP for the FP group was significantly higher than PP or HP ($p < 0.01$) (Table 2). As a result of improved

hemostasis, the amount of resuscitation fluid administered to restore the target MAP was significantly less in the FP group compared with PP and HP ($p < 0.01$) (Table 2). This difference in the volume of fluid infused is reflected in HCT measurement at the end of the study or at death in the three groups (11 ± 1.1 , 3 ± 1.0 , and 2 ± 0.1 in FP, HP, and PP, respectively).

Survival after the 120-minute postinjury observation period for FP, PP, and HP was 89% (8 of 9), 0% (0 of 9), and 13% (1 of 8), respectively. FP improved percent survival significantly compared with PP and HP ($p < 0.01$). Likewise, a significant increase in total survival time was observed in the FP group (111 minutes ± 9 minutes) compared with PP (39 minutes ± 4 minutes) and to HP (41 minutes ± 12 minutes) ($p < 0.01$). Dressing adherence strength was significantly higher in the FP group (diaphragmatic 1.8 kg ± 0.21 kg, visceral 1.4 kg ± 0.35 kg) than in the PP group (diaphragmatic 0.2 kg ± 0.04 kg, visceral 0.1 kg ± 0.03 kg) ($p < 0.01$).

DISCUSSION

The animal model used in this study involves extensive parenchymal and vascular damage in the liver. The injury damages vascular structures that are similar to human with approximately 1 cm in diameter. It is well documented that in human trauma, injury to major abdominal veins, such as the portal and hepatic veins, is associated with significant hemorrhage and subsequent mortality.¹³ Coagulopathy makes the challenge of achieving and maintaining hemostasis in these patients even greater. The association of hypothermia, and coagulopathy with high mortality in trauma patients has been well described.¹⁴ As many as 66% of severely injured trauma patients who require intubation arrive in emergency departments manifesting hypothermia (temperature $<36^{\circ}\text{C}$).¹⁵ Approximately 80% of nonsurviving patients receiving massive transfusions have a body temperature of less than 34°C .¹⁶ Furthermore, investigators have reported a 2.4-fold increase of blood loss in postlaparotomy patients whose body temperature was $33.8^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ compared with patients whose temperature was $36.1^{\circ}\text{C} \pm 0.7^{\circ}\text{C}$ despite similar injury severity.¹⁷ We think that this complex animal model is an excellent means to study this extreme pathophysiologic, traumatic state and also provides relevance and insight into other severe low pressure/high flow bleeding situations encountered by surgeons.

Although recent studies challenge current resuscitation practices,¹⁸ no regimen is ideal. Often, the interventions iatrogenically induce or complicate the situation. Massive hemorrhage presents a host of challenges that quickly compound into life-threatening and difficult-to-manage clinical situations. Therefore, the earlier the bleeding is controlled, the better the chances of preventing morbidity and mortality. Although coagulopathy actually begins with the initial bleeding when coagulant proteins and PLTs are directly lost from the vasculature at the site of bleeding, trauma patients still

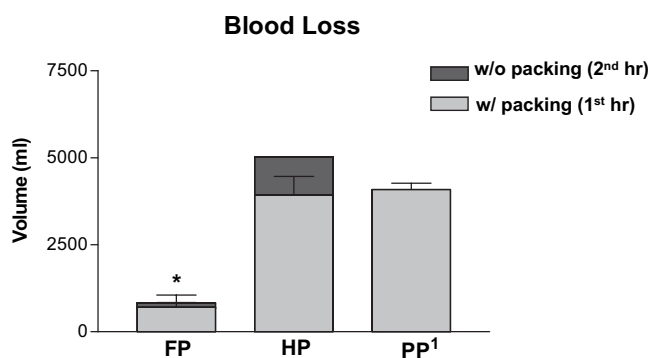


Fig. 1. Postinjury blood loss of cold and coagulopathic swine with grade V liver injury, treated with fibrin patch (FP, $n = 9$) plus packing, placebo patch (PP, $n = 9$) plus packing or hepatic packing (HP, $n = 8$) alone. Each column represents bleeding volumes during the first hour of observation with packs in place and during the second hour of observation after packs were removed. *Statistically significant from HP or PP group, $p < 0.01$. All the animals in PP group died before the 60-minute time point, therefore there was no bleeding in the second hour after the removal of packs.

have 60% of their coagulation factors when they have lost approximately 40% of their blood volume.¹⁹ But uncontrolled bleeding demands replacement of the lost volume. This is commonly achieved with crystalloid resuscitation fluids and packed red blood cells, which leads to further dilution of remaining clotting factors, further impairing the coagulation system. Hypothermia additionally impairs the activity of enzymes in the clotting cascade. Studies have shown that even correcting the hypothermia does not fully reverse the coagulopathy.²⁰ All of these circumstance are further complicated in a military trauma setting.²¹ Surgeons often implement “damage control,”²² but to be successful, bleeding must be stopped rapidly. This study showed that successful hemorrhage control (hemostasis) results in conserving resuscitation fluid and maintaining HCT, PLTs, and blood pressure. Conservation of red blood cells translates into higher oxygen transport to vital tissues. Crucial in trauma damage control operation, the reduction in resuscitation fluid requirement also prevents any further derangement in the coagulopathy.²³

The coagulopathy induced in this model is a multimodal one. This model combines dilutional and hypothermic effects on the animals’ coagulation system. This is of clinical relevance as indicated by changes in a variety of coagulation function tests (ACT, PT, aPTT, and FIB), decreases in HCT and PLT, and a lower body temperature. The isovolemic hemodilution induced in this model resulted in a 49% decrease in HCT from baseline to preinjury. The use of Hextend to produce hemodilution and to resuscitate the animals after liver injury and hemorrhage may have produced a greater degree of coagulopathy than crystalloids. The colloid fluids particularly those that contain high molecular weight hydroxyethyl starch may force the relocation of coagulation proteins including FIB from the plasma volume into interstitial space, thereby depleting blood of clotting factors.²⁴ Moreover, Hextend may transiently alter the coagulation function by a direct inhibition of factor VIII activity, producing an acquired, reversible von Willebrand’s-like syndrome.^{25,26} These effects of Hextend may have produced even more severe coagulopathic bleeding to be controlled by the hemostatic treatments (i.e. FP) in this study. It should be mentioned that the use of Hextend with high oncotic effect, which limited resuscitation volume, was mandatory in this model. In our preliminary experiments, when a crystalloid (lactated Ringer’s solution) was used for resuscitation, target blood pressure often could not be achieved despite a successful hemostatic treatment. This resulted in excessive fluid administration to the animals, massive tissue edema, and occasional death that was not related to blood loss but was likely because of extreme hemodilution.

The grade V liver injury and subsequent uncontrolled hemorrhage generated in this model as well as the peri-HP have been used many times in previous studies at this institute and others.^{8,9,27,28} The model is very consistent and reproducible, evidenced by the low variance and consistent mean values across all treatment groups for preinjury MAP (79 mm

Hg \pm 1 mm Hg), injury score (2.0 ± 0.2), pretreatment blood loss (511 mL \pm 30 mL), resuscitation target MAP (63 mm Hg \pm 1.1 mm Hg), and number of laparotomy packing sponges used per animal (12.3 ± 0.2).

CONCLUSIONS

The FP hemostatic dressing used with HP demonstrated an overall improvement in ability to achieve hemostasis in a cold, coagulopathic swine model compared with HP alone or the placebo patch with HP. The effect was durable, as the FP hemostatic dressing was able to maintain hemostasis for an additional hour once the HP was removed. The ability of this dressing to effectively control and maintain hemostasis in this complex challenging model, especially when compared with the current standard of care (HP), demonstrates that this product can serve as a novel hemorrhage control tool that could improve the outcome of patients with coagulopathic traumatic injuries both in civilian and military settings. After successful hemostasis the additional benefit of this reabsorbable dressing is that it could be left in a patient’s body cavity after treatment, eliminating or reducing the need for additional surgery to remove hemostatic material. For the patient this could translate into a reduction in intensive care unit stay, rate of infection, morbidity, mortality, and overall cost. Overall, this biologic hemostatic dressing proved to effectively control coagulopathic bleeding and to prevent death in a model of grade V liver injury in which the current standard of care was ineffective.

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Editor's Note: Due to a transcription error, the discussion by P.J. Schenarts, MD and others for this paper will not appear.